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Controversies in Lymphoma: The Role of Hematopoietic Cell Transplantation for Mantle Cell Lymphoma and Peripheral T Cell Lymphoma

Peter Dreger,[1] *Ginna G. Laport*[2]

[1] Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany; and [2] Division of Blood and Marrow Transplantation, Stanford University Medical Center, Stanford, California

Correspondence and reprint requests: Ginna G. Laport, MD, Division of Blood and Marrow Transplantation, Stanford University Medical Center, 300 Pasteur Drive, Rm H3249, Stanford., CA 94305-5623 (e-mail: glaport@stanford.edu).

ABSTRACT

Mantle cell lymphoma (MCL) and peripheral T cell lymphoma (PTCL) are distinct lymphoma subtypes that each comprise about ~10% of the non-Hodgkin lymphomas. Although both subtypes are characterized by high remission rates to frontline chemotherapy, the prognosis is generally poor because of inevitable relapse within 1-2 years or less, depending on the specific histology. Patients with MCL who achieve a complete remission with upfront conventional chemotherapy currently have several options for consolidative therapy including maintenance therapy with rituximab, autologous hematopoietic cell transplantation (HCT), and more recently, allogeneic HCT utilizing a reduced intensity conditioning (RIC) regimen. In the autologous HCT setting, the added efficacy of rituximab is under active investigation as a method of *in vivo* purging during hematopoietic cell mobilization, as part of the conditioning regimen and as post-HCT maintenance therapy. For patients with PTCL, autologous HCT is commonly offered at relapse but there are a few prospective series utilizing autologous HCT as consolidation of CR1 with encouraging results. There is no conclusive evidence regarding the efficacy of allogeneic HCT, but outcomes with RIC regimens appear promising. This review summarizes the current role of HCT for patients with MCL in first remission and for patients with PTCL as consolidation and for relapsed/refractory disease.

KEY WORDS

Mantle cell lymphoma • Peripheral T cell lymphoma • Hematopoietic cell transplantation • Autologous • Allogeneic

MANTLE CELL LYMPHOMA

Mantle cell lymphoma (MCL) is an aggressive B cell lymphoma that is characterized by early dissemination and an unfavorable clinical course. Because the results of standard lymphoma first-line therapy are disappointing with a median relapse-free survival (RPS) of <2 years even with incorporation of rituximab, a variety of postremission consolidation strategies is under investigation [1-3]. Essentially, these are based on 3 elements proven to be effective in MCL during recent years: antibody maintenance, high-dose ara-C intensification, and autologous and allogeneic hematopoietic cell transplantation (autoHCT, alloHCT).

Allogeneic HCT and the Role of Rituximab

To improve the dismal prognosis of MCL, myeloablative therapy with autoHCT has been extensively studied since the early nineties. The Nebraska group was first to show the potential efficacy of this intensive modality in MCL [4]. Since then, numerous studies have been published documenting feasibility and potent antilymphoma activity of autoHCT in this entity, in particular, if used as part of first-line treatment [5-7]. However, almost all trials were uncontrolled and suffered from small patient numbers and limited observation times. Only recently were Dreyling and coworkers [8] able to demonstrate superiority of autoHCT over standard CHOP (cyclophosphamide, doxorubin, vineristine, prednisone) chemotherapy with interferon maintenance in terms of progression-free survival (PFS) in a prospective randomized phase III study. Nevertheless, with a median follow-up of 34 months, a plateau in the survival curve was not seen, and a significant survival benefit could not be shown.

With the availability of rituximab (RTX), it soon became evident that this monoclonal antibody (mAb) was also effective in MCL. The addition of RTX to standard CHOP chemotherapy yielded promising response rates, and resulted in significantly prolonged times to treatment failure in a prospective randomized study, although PFS and overall survival (OS) were not improved [2,9].

Another modality with strong activity in MCL is represented by intensive ara-C-containing combination chemotherapy regimens, such as Hyper-CVAD/Mtx-HA (methotrexate and high-dose ara-C), DHAP, HAM, and Dexa-BEAM. This conclusion was initially based on the observation that these regimens used alone or sequentially after CHOP consistently yielded response rates of 90% or more [6,10-12]. A second line of evidence derives from minimal residual disease (MRD) studies documenting a median reduction of the tumor load of more than 1 log with Dexa-BEAM, whereas CHOP-like regimens had no significant impact on MRD [13].

Further improvement of first-line treatment results could be achieved by combinations of these 3 MCL-active modalities (rituximab, HA, and autoHCT). The M.D. Anderson group examined the combination of RTX with repetitive hyper-CVAD/Mtx-HA as first-line treatment of MCL in a large prospective phase II trial. With an 87% complete remission (CR) rate, failure-free survival (FFS) after 3 years was 64%, and thus comparable to results achieved with sequential HA-autoHCT. However, because the toxicity of this regimen was substantial, with 5% toxic deaths and a number of secondary t-MDS, it does not appear to have significant advantages over autoHCT [14]. Two small studies investigated the combination of autoHCT with RTX maintenance as part of first-line treatment not including HA [15,16]. Disease control was very promising, although the results must be regarded as preliminary because of low patient numbers and short observation times. More experience has been gained with the triple combination rituximab-HA-autoHCT using RTX mainly pre-HCT for *in vivo* purging. Although follow-up was limited, PFS appeared to be consistently higher than 60% after 3 years [10,17,18]. The Nordic lymphoma group reported the results of 2 subsequent prospective phase II trials with first-line treatment of MCL [19]. Forty-two patients were entered on a protocol consisting of 3 cycles of intensified CHOP. Responders were consolidated with BEAM followed by autoHCT. With an overall response rate of 74% to CHOP, FFS after 3 years was 24%. Subsequently, the regimen was intensified by addition of 2 rounds of HA after CHOP and 2 doses of RTX for *in vivo* purging prior to hematopoietic stem cell collection. By the time of reporting, 130 evaluable patients were enrolled on the second protocol. Overall response to CHOP-rituximab-BEAM was 91%, translating to a 3-year FFS of 67%, which was significantly superior to the first protocol. Meanwhile, this trial has been completed with preliminary results confirming a plateau in FFS survival above 60% (C. Geisler, personal communication, September 2007).

To date, however, the most compelling evidence for a beneficial effect of adding RTX to the HA-autoHCT sequence is provided by a study analyzing the effect of 2 doses of peritransplant RTX in first-line autoHCT in MCL. In a prospective phase II design, patients with newly diagnosed MCL were treated with a sequential dose-escalating therapy comprising standard chemotherapy for remission induction, intensive ara-C-containing chemotherapy for mobilization of hematopoietic stem cells, and myeloablative therapy followed by autoHCT. The myeloablative regimen consisted of total body irradiation (TBI) and high-dose cyclophosphamide supplemented with 2 doses (375 mg/m^2) of RTX. Outcome parameters (toxicity, clinical, and molecular response as assessed by allele-specific *IGH* real-time PCR, event-free survival (EFS), and OS were compared with those of 34 historic controls treated identically but without RTX. Thirty-four patients were accrued. Results were initially analyzed as of April 2006, and updated for the purpose of this Education Supplement with a median follow-up of 38 (6-104) months for the RTX group and 90 (4-174) months for the controls [20]. EFS was significantly increased with peritransplant RTX (Figure 1). This was associated with a trend for a superior molecular response rate in 11 study patients versus 10 control patients with an available marker (73% versus 30%, $P = .086$). In a subsequent study, we showed that results could be further improved by RTX maintenance therapy instead of peritransplant RTX (Rieger et al., unpublished). This was consistent with the favorable outcome observed in the previously mentioned 2 phase II studies including short-term RTX maintenance [15,16]. An advantage of posttransplant RTX is also suggested by results from the Nordic Lymphoma Group trials indicating that MRD recurrence after autoHCT can be ameliorated by preemptive infusion of RTX [19].

Allogeneic HCT

Another potentially curative option is consolidation with alloHCT after having achieved response with effective primary therapy including autoHCT [21]. The rationale of alloHCT stems from the possibility of superior antilymphoma efficacy because of the graft-versus-lymphoma effect associated with alloHCT. Compared to autoHCT, relapse rates appear to be lower after alloHCT, but this has not translated into a superior OS because of significant nonrelapse mortality (NRM) even with reduced-intensity conditioning (RIC). Considering the good outcome data with antibody-/autoHCT-based consolidation, the

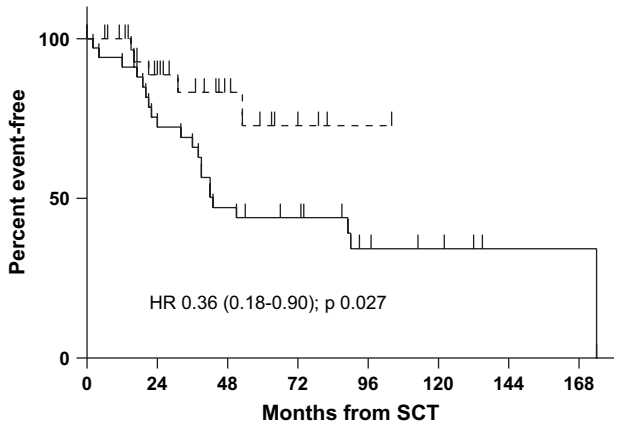

Figure 1. Updated EFS following autoSCT after myeloablative therapy with (broken line, n = 34) or without peritransplant rituximab (solid line, n = 34).

advanced age of the patients, the toxicity of alloHCT, and the paucity of data in favor of first-line alloHCT (Table 1), this procedure cannot be regarded as evidence-based treatment for MCL in first CR, and should be only performed within clinical trials. A strategy of reserving alloHCT for second-line therapy is further supported by the fact that, in contrast to autoHCT, alloHCT can also yield favorable results in the salvage setting [22,23].

FUTURE DIRECTIONS

Beyond these established modalities, more recent innovations with documented activity in MCL, such as radioimmunotherapy, proteasome inhibitors, mTOR inhibitors, and "small molecules," promise to further enhance the efficacy of therapy. With regard to radioimmunotherapy, both Y^{90} ibritumomab tiuxetan and and I^{131} tositumomab have been shown to be safe and effective when used together with high-dose etoposide and cyclophosphamide for myeloablation prior to autoHCT in relapsed or refractory MCL [24,25]. The German Lymphoma Study Group is currently performing a phase II trial with Y^{90} ibritumomab tiuxetan/high-dose cyclophosphamide myeloablation followed by autoHCT in relapsed MCL. More recently, the therapeutic efficacy of the proteasome inhibitor, bortezomib, in MCL has been investigated. Whereas single-agent bortezomib appears to be clearly inferior to accepted standard regimens when used as first-line treatment, it may have a place in the salvage setting or in combination with other MCL-active compounds [26-28]. Other novel drugs with potential efficacy in MCL are temsirolimus, everolimus or *BCL-2* inhibitors [29-31]. However, none of these agents alone or in combination has an established place in first-line treatment of MCL to date.

Taken together, with modern treatment approaches including autoHCT and rituximab, the prognosis of MCL at least in younger patients today has dramatically improved compared to the old days of CHOP monotherapy. Continuing innovation in this field makes cure of this disease even without allogeneic HCT a realistic goal.

PERIPHERAL T CELL LYMPHOMAS: INTRODUCTION

The peripheral T cell lymphoma (PTCL) represent a heterogeneous group of lymphomas and account for approximately 10% to 15% of the non-Hodgkins

Table 1. *Allogeneic SCT for Mantle Cell Lymphoma*

Study	Design	n	CR1 (%)	MSD (%)	TCD (%)	Conditioning (n)	Follow-up (months)	2-y NRM	2-y DFS	2-y OS
Khouri et al. [21]	phase II;	16	31%	94%	0	TBI/Cy (11) BEAM (3) Fu/araC/cisplatin (2)		6 of 16	55% (3 y)	55% (3 y)
Laudi et al. [52]	phase II	17	29%	79%	0	TBI/Cy (10) Fu/Bu/TBI (3) Fu/Cy/TBI (4)	31	29%	50%	49%
Ganti et al. [53]	retrospective	17	n.a.	100%	0	TBI/Cy (15) TBI/Cy (1) Bu/Cy (1)	33	19% (3 mo)	53%	58%
Reduced intensity conditioning										
Maris et al. [22]	phase II;	33	0	48%	0	TBI2/F	25	24%	60%	65%
Robinson et al. [54]	registry	22	n.a.	n.a.	n.a.	RIC miscellaneous	9	82%	0	18%
Khouri et al. [23]	phase II	18	0	72%	0	FC-R (13) Fu/araC/cisplatin (5)	26	2 of 18	82%*	86% (3 y)
Morris et al. [55]	phase II	10	n.a.	n.a.	100%	Fu/Mel/CD52	36	20%	50% (3 y)	60% (3 y)

BEAM indicates carmustine, etoposide, ara-C, high-dose melphalan; Bu, busulfan; CD52, alemtuzumab; CR1, first complete remission; Cy, high-dose cyclophosphamide; DFS, disease-free survival; Fu, fludarabine; FC-R, fludarabine, cyclophosphamide, rituximab; Mel, high-dose melphalan; RIC, reduced-intensity conditioning; TBI/Cy, total body irradiation, high-dose cyclophosphamide; TBI2, low-dose TBI; NRM, nonrelapse mortality; OS, overall survival; MSD, matched sibling donor; TCD, T cell depletion; y, years; mo, months.

*Current progression-free survival.

lymphomas (NHL). According to the WHO/EORTC classification, there are 9 distinct clinicopathologic subtypes with distinct characteristics and varied clinical courses. The most common subtypes are PTCL-unspecified (PTCL-u) and anaplastic large cell lymphoma (ALCL), which comprise approximately 50% and 25% of all PTCL histologies, respectively. Compared to the B cell lymphomas, PTCL tends to present in extranodal sites and generally carry a poorer prognosis with 5-year survival of <30% [32]. One exception, however, are patients with anaplastic lymphoma kinase (ALK)-positive anaplastic ALCL where 5-year survival reaches 60% to 90% after conventional therapy [33]. Despite less than optimal results, frontline chemotherapy with CHOP or CHOP-like regimens remain the most commonly used regimens with more intensive regimens such as hyperCVAD unable to significantly improve upon these results [34].

Regarding the role of HCT, it is difficult to draw definitive conclusions about the efficacy of HCT in this patient population because of the low incidence of this disease and the heterogeneity of the subtypes. Numerous reports detailing HCT for PTCL have been published, but most series are of small sample sizes with various histologies. The utility of alloHCT is less definitive, as there are very few reports specifically utilizing this modality and most alloHCT cases are intermingled with autoHCT reports. The following report summarizes published experience with autoHCT and alloHCT for patients with PTCL.

Autologous HCT

High-dose chemotherapy with autoHCT for relapsed/refractory aggressive B cell lymphomas offers the best chance for long-term survival in patients with chemosensitive disease. However, its efficacy for patients with relapsed/refractory PTCL is less clearly defined, as no prospective HCT trial has been conducted and patients with PTCL comprise a small proportion in most HCT reports for aggressive NHL. Given the poor prognosis of most PTCL subtypes, autoHCT has been offered as consolidation of first remission (CR1) and for patients with relapsed and refractory disease.

RELAPSED/REFRACTORY DISEASE

The majority of published case series describes the results of autologous HCT in the relapsed/refractory setting with PTCL-u and ALCL being the predominant subtypes in these trials (see Table 2). Several pre-HCT factors identified that aid in predicting outcome after autoHCT include chemosensitivity, pretransplant International Prognostic Index (IPI) (score, pretransplant lactate dehydrogenase [LDH]), disease status, beta-2-microglobulin and histology [35-38]. One of the largest series published to date comes from the Spanish GEL-TAMO (Grupo Espanol de Linfomas/Transplante Autologo de Medula Osea) group [36]. This was a heterogeneous group of 115 patients in which approximately 32% of patients were in CR1 at the time of HCT with the rest of the patients being beyond CR1 or with refractory disease. With a median follow-up of 37 months, the 5-year OS and disease-free survival (DFS) for all patients was 56% and 60%, respectively. For the patients transplanted in CR1, the OS and DFS at 5 years were both ~80%, in contrast to the 6 patients with refractory disease, who had an OS of 0%. Pre-HCT factors that correlated with outcome were LDH, age-adjusted IPI, and disease status. A recent retrospective study from the BSBMT (British Society of Bone Marrow Transplant) and the ABMTRR (Australian Bone Marrow Transplant Recipient Registry) of 64 patients with PTCL also identified chemosensitivity as the most important predictor for both PFS and OS by multivariate analysis [37]. The 3-year PFS and OS were 50% and 53%, respectively, with a median OS of 52 months. Patients with chemosensitive disease had a 3-year OS of 58%

Table 2. *Autologous Hematopoietic Cell Tranplantation for Relapsed/Refractory Peripheral T Cell Lymphoma*

Group/Year	n	Median Age (Range)	Preparative Regimen	DFS/PFS	OS	Follow-up	Relapse	TRM
BSMT/ABMTRR [37] 2007	64	51 y (17-70)	varied	50	53	37 mo	32	9
Cleveland Clinic [43] 2007	32	44 (16-69)	Bu/VP16/Cy	18	34	30 mo	69	NR
South Korea [56] 2007*	40	44 (18-68)	BEAM,BEAC others	25	46	16 mo	58	NR
MSKCC [38] 2006	24	48 (24-73)	varied	24	33	72 mo	83	NR
Vanderbilt [42] 2004*	28	39 (8-60)	TBI/Cy/VP16,	50	69	3y	32	NR
GEL-TAMO [36] 2003*	115	41 (13-72)	BEAM,BEAC	51	56	37 mo	NR	8
Princess Margaret [57] 2003	36	46 (19-62)	Mel/VP16,TBI/VP/Mel	37	48	42mo	NR	17
Sweden [40] 2001	40	42 (16-61)	BEAM, BEAC others	48	58	25mo	NR	8

BSMBT indicates British Society of Bone Marrow Transplantation; ABMTRR, Australian Bone Marrow Transplant Recipient Registry; MSKCC, Memorial Sloan Kettering Cancer Center; GEL-TAMO, Grupo Espanol de Linfomas/Transplante Autologo de Medula Osea; bu, busulfan; Cy, cyclophosphamide; Mel, melphalan; DFS/PFS, disease-free survival/progression-free survival; OS, overall survival; mo, months; y, years; UK, United Kingdom; TBI, total body irradiation; BEAC, carmustine, etoposide, cytarabine, cyclophosphamide; BEAM, carmustine, etoposide, cytarabine, melphalan; TRM, treatment-related mortality; NR, not reported.

*Includes first remission patients.

Table 3. *Autologous Hematopoietic Cell Transplantation as Frontline Therapy for Peripheral T Cell Lymphoma*

Group/Year	n	Median Age (Range)	Preparative Regimen	DFS/PFS	OS	Follow-up	TRM
GEL-TAMO [58] 2003	74	46 (15-69)	BEAM,BEAC Cy/TBI, CBV	63	68	67mo	4
Italy [48] 2006	62	43 (20-60)	Mitoxantrone/Mel,BEAM	30	34	76mo	5
GELA [59] 2004	52	39 (16-60)	CBV, BEAM	NR	44	6.5y	NR
Germany [47] 2004	30	46 (30-62)	TBI/Cy	Not reached	Not reached	15mo	3

GEL-TAMO indicates Grupo Espanol de Linfomas/Transplante Autologo de Medula Osea; GELA, Groupe d'Etude des Lymphomas de l'Adulte; Cy, cyclophosphamide; DFS/PFS, disease-free survival/progression-free survival; OS, overall survival; BEAC, carmustine, etoposide, cytarabine, cyclophosphamide; BEAM, carmustine, etoposide, cytarabine, melphalan; Mel, melphalan; TBI, total body irradiation; TRM, treatment-related mortality; CBV, cyclophosphamide, carmustine, VP16. mo, months; y, years.

versus 36% for patients with chemorefractory disease ($P = .007$).

The age-adjusted IPI at the time of relapse, also known as the second line age-adjusted IPI (sAA-IPI), has been identified as an important prognostic factor prior to HCT. Investigators from Memorial Sloan Kettering reported the outcomes of 24 PTCL patients with relapsed or primary refractory disease but excluded patients with ALK-positive ALCL [38]. With a median follow-up of 6 years, the 5-year PFS and OS were 24% and 33%, respectively, with disease progression occurring in 83% of patients. The sAA-IPI was the only variable significant for both PFS and OS in multivariate analysis. Interestingly, when these outcomes were compared to 86 consecutive patients with chemosensitive relapsed or primary refractory diffuse large B cell lymphomas, there was no significant difference with respect to disease progression or survival after progression when stratified by the sAA-IPI. This finding suggests that autoHCT may overcome the adverse prognosis associated with T cell histology in the relapsed setting. The GEL-TAMO group also found that sAA-IPI correlated with survival among PTCL patients who achieved less than a CR after induction chemotherapy [39]. However, IPI at the time of initial diagnosis does not appear to impact outcome after autoHCT [40,41].

Among the PTCL subtypes, the impact of histologic subtype on outcome after HCT is less defined with the exception of patients with ALK+ ALCL who typically have superior survivals compared to those with non-ALCL histologies. ALCL patients comprise a subgroup of PTCL with higher CR rates and improved OS, and thus, the role of autoHCT is more appropriate in the relapsed setting. In a series of 28 relapsed PTCL patients from Vanderbilt University, investigators aimed to determine if histology impacted the outcomes of 28 relapsed PTCL patients after autoHCT [42]. The 3-year EFS and OS were 69% and 50%, respectively, but when ALCL patients were analyzed separately, the 3-year OS was 86% compared to 47% for the non-ALCL patients ($P = .01$). The ALK-positive ALCL patients fared best, with an EFS of 100% versus 0% compared to ALK-negative ALCL. Furthermore, in a Norwegian study of 40 patients with PTCL, the subgroup of 14 patients with ALCL also showed a trend for better OS compared to the other PTCL histologies, 79% versus 44%, $P = .08$ [40]. Another recent report of 32 PTCL patients did not demonstrate a survival advantage for the ALCL patients, although the ALK status was known only in about half of the 21 ALCL patients [43]. Thus, most published results so far indicate that a high proportion of relapsed ALK+ ALCL patients are cured with autoHCT.

A few reports from Europe have described the results of autoHCT specifically for angioimmunoblastic T cell lymphoma (AITL), a rare and aggressive subtype that usually affects older patients and is characterized by systemic disease with lymphadenopathy, fever, weight loss, ascites, and polyclonal gammopathy. Prognosis is poor, with a long-term survival rate of 10% to 30% and a median survival of <3 years [44]. The Spanish GEL-TAMO group described the results with autoHCT in 19 AITL patients, most of whom were in CR1 and reported a 3-year PFS and OS of 55% and 60% [45]. A similar report from an EBMT retrospective analysis in 29 AITL patients showed a 5-year EFS and OS of 37% and 44%, with nearly half of the patients in CR1 at the time of HCT [46]. The achievement of CR after HCT was a favorable prognostic factor, as those patients experienced an OS of 62%. Thus, autoHCT may improve the survival of AITL patients, especially if offered HCT in CR1.

FIRST REMISSION

Given the poor outcomes after conventional chemotherapy, the role of HCT as consolidation therapy in CR1 has been explored. Four published reports to date (see Table 3) demonstrate the feasibility of autoHCT as consolidation therapy. The first prospective PTCL-restricted multicenter study incorporating autoHCT as part of first-line therapy accrued 30 patients with various PTCL histologies [47]. Patients received 4-6 cycles of CHOP followed by further induction chemotherapy prior to autoHCT with a preparative regimen of TBI and cyclophosphamide. Twenty-one

patients (70%) proceeded to HCT with a 100% CR rate after HCT. With a 15-month median follow-up, 76% of the HCT patients remained in CR. Progressive disease was the main obstacle in proceeding to HCT. A report from Italy of 68 PTCL patients with a lengthy follow-up of over 6 years combined the results of 2 prospective phase 2 trials investigating the role of high-dose sequential chemotherapy followed by autologous HCT in 62 patients with advanced stage PTCL [48]. The 12-year EFS and OS was a disappointing 30% and 34%, respectively, for all patients. However, the subset of ALK positive patients fared better with a 12-year OS of 62%. Multivariate analysis showed that achievement of CR prior to HCT was a statistically significant factor in terms of EFS and OS ($P < .0001$), indicating the importance of chemosensitivity. This was an intent-to-treat analysis, and it should be mentioned that 26% of patients did not proceed to HCT because of progressive disease as in the previously mentioned German study. The Spanish GELTAMO group published a large retrospective series of 75 PTCL patients using autoHCT as consolidation in CR1 [49]. The PTCL-u histology comprised 50% of patients with ALCL patients being the second most frequent histology (30%). The 5-year PFS and OS was an encouraging 63% and 68%, respectively, for all patients. When the outcomes of the ALCL patients were compared to the non-ALCL histologies, the PFS and OS were significantly superior (80% versus 55%, $P = .03$ and 84% versus 61%, $P = .058$, respectively) despite the fact that the ALK status was not available in most of the ALCL patients. In summary, autoHCT as a frontline therapy is a reasonable option for PTCL patients considering their inherently poor prognosis. Current data shows that this modality may increase the OS of such patients compared to conventional therapy. However, for ALK+ ALCL patients who carry a more favorable prognosis, HCT should be reserved in the event of relapse or for induction failures.

Allogeneic HCT

The experience with alloHCT for PTCL is limited to only a few published studies with small numbers of patients. One of the larger series comes from the BSBMT and ABMTRR group in which 18 patients underwent myeloablative allogeneic HCT [37]. Nine patients had PTCL-u, with the rest having ALCL, T cell leukemia, and cutaneous T cell lymphoma. Thirteen (72%) patients received grafts from matched-related donors. With a median follow-up of nearly 6 years, the PFS and OS was 33% and 39%, respectively, with a 3-year relapse rate of 39%. Although the median age of this group was only 28 years old (range: 2-52 years old), the TRM of 38% was significant. In a Japanese report of 28 patients, 23 patients underwent myeloablative conditioning with 5 patients receiving a reduced intensity regimen. The 2-year PFS and OS of 34% and 40%, respectively, but the TRM was 30% for the myeloablative recipients and 20% for the RIC recipients [50]. RIC regimens, however, may show more promise with less toxicity [51]. An Italian group conducted a prospective phase II trial utilizing a RIC regimen with fludarabine (Flu), thiotepa, and cyclophosphamide in 17 patients with refractory or relapsed disease. This regimen was well tolerated, with an NRM of 6% at 2 years. The 3-year PFS and OS was an encouraging 64% and 81%, respectively. Four patients received DLI, with responses seen in 2 patients suggesting the existence of a graft-versus-lymphoma effect.

SUMMARY

HCT is being increasingly offered to patients with MCL and PTCL as consolidation in CR and for relapsed disease. For MCL patients in CR1, the efficacy of autoHCT appears to be improved especially when RTX is incorporated in the peritransplant period. Evidence exists for a graft-versus-lymphoma effect in MCL and early results with allogeneic RIC regimen appear encouraging, although NRM incidence is variable among published series. The role of autoHCT as part of induction therapy in PTCL is still under debate, but given the inherently poor prognoses of most T cell histologies, it is reasonable to offer HCT early in their treatment course. Patients with a high-risk IPI at the time of diagnosis should be considered for autoHCT or perhaps RIC alloHCT as consolidation of CRI. AutoHCT for relapsed PTCL appears to benefit those with chemosensitive disease, especially patients with ALK+ ALCL. For both MCL and PTCL, only large prospective studies in the multicenter setting with lengthy follow-up will have the ability to truly measure the impact of HCT in these aggressive disease entities.

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